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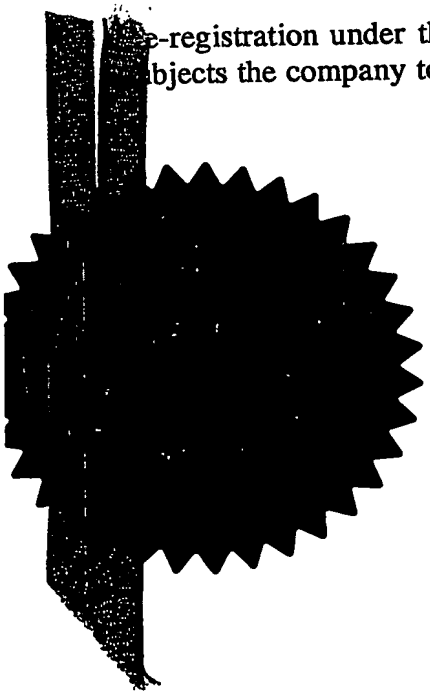

Signed P. Mahoney

Dated 9 October 2003

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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Cardiff Road
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1. Your reference — N.86391 GCW/RCS

2. Patent application number
(The Patent Office will fill in this part) — 20 SEP 2002 — 0221923.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ARROW THERAPEUTICS LIMITED
Britannia House
7 Trinity Street
London SE1 1DA

Patents ADP number *(if you know it)* 07108217002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)* — J.A. KEMP & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

14 South Square
Gray's Inn
London
WC1R 5JJ

Patents ADP number *(if you know it)* 00000026001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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Continuation sheets of this form	0
Description	61
Claim *(s)*	9
Abstract	1
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature J.A. Kemp & Co Date 20 Sept 2002

J.A. KEMP & CO.

12. Name and daytime telephone number of person to contact in the United Kingdom

SRINIVASAN, Ravi Chandran
020 7405 3292

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DUPLICATE

CHEMICAL COMPOUNDS

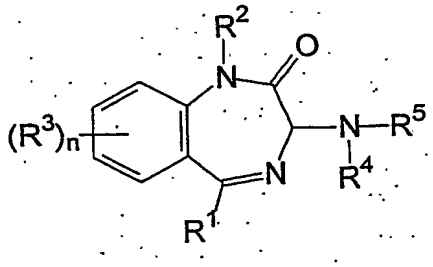
The present invention relates to a series of benzodiazepine derivatives which are active against Respiratory Syncytial Virus (RSV).

RSV is a major cause of respiratory illness in patients of all ages. In adults, it tends to cause mild cold symptoms. In school-aged children, it can cause a cold and bronchial cough. In infants and toddlers it can cause bronchiolitis (inflammation of the smaller airways of the lungs) or pneumonia. It has also been found to be a frequent cause of middle ear infections (otitis media) in pre-school children. RSV infection in the first year of life has been implicated in the development of asthma during childhood.

Current anti-RSV therapy involves the use of a monoclonal antibody to RSV, called palivizumab. However, although this antibody is often effective, it is expensive. Indeed, its expense means that it is unavailable for many people in need of anti-RSV therapy. There is therefore an urgent need for effective alternatives to existing anti-RSV therapy.

It has now surprisingly been found that the particular benzodiazepine derivatives of the general formula (I) set out below are active against RSV.

Accordingly, the present invention provides, in a first embodiment, the use of a benzodiazepine derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or preventing an RSV infection



(I)

wherein:

R^1 represents C_{1-6} alkyl, aryl or heteroaryl;

- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, -NH-CO-R', $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- R^5 represents C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-XR^6$;
- X represents -CO-, -S(O)- or $-S(O)_2$-; and
- R^6 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-. Typically, R' and R'' are not both hydrogen.

As used herein, a C_{1-6} alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_{1-4} alkyl group or moiety. Examples of C_{1-4} alkyl groups and moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl and *t*-butyl. For the avoidance of doubt, where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.

As used herein, an acyl group is a C_{2-7} acyl group, for example a group -CO-R, wherein R is a said C_{1-6} alkyl group.

As used herein, an aryl group is typically a C_{6-10} aryl group such as phenyl or naphthyl. Phenyl is preferred. An aryl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substitutents on an aryl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbomyl, amino,

mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR'R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR'R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl.

Preferred substituents on an aryl group include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

As used herein, references to an aryl group include fused ring systems in which an aryl group is fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group. Preferred such ring systems are those wherein an aryl group is fused to a heterocyclyl or heteroaryl group. Examples of such fused ring systems are groups in which a phenyl ring is fused to a thienyl group or to a tetrahydrofuranyl group to form a benzothienyl or dihydrobenzofuranyl group.

As used herein, a carbocyclyl group is a non-aromatic saturated or unsaturated monocyclic hydrocarbon ring, typically having from 3 to 6 carbon atoms. Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopentyl or cyclohexyl. A cycloalkyl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substitutents on a carbocyclyl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbomyl, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR'R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR'R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl.

Preferred substituents on an carbocyclyl group include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

As used herein, a heterocyclyl group is a non-aromatic, monocyclic saturated or unsaturated carbocyclic ring typically having from 5 to 10 carbon atoms,

in which one or more, for example 1, 2 or 3, of the carbon atoms is replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples include tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, dioxolanyl, thiazolidinyl, tetrahydropyranyl, piperidinyl, dioxanyl, piperazinyl, morpholinyl, thiomorpholinyl and thioxanyl. Piperazinyl, piperidinyl and morpholinyl are preferred. A heterocyclic group may be unsubstituted or substituted at any position. Typically, it carries 0, 1 or 2 substituents.

Suitable substitutents on a heterocyclyl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbomyl, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR'R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR'R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl.

Preferred substituents on a heterocyclyl group include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro. Most preferably, a heterocyclyl group is unsubstituted or substituted by one or two C_{1-2} alkyl groups.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine and is preferably chlorine or fluorine.

As used herein, an alkoxy group is typically a said alkyl group attached to an oxygen atom. An alkylthio group is typically a said alkyl group attached to a thio group. A haloalkyl or haloalkoxy group is typically a said alkyl or alkoxy group substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as $-CX_3$ and $-OCX_3$ wherein X is a said halogen atom, for example chlorine or fluorine. Particularly preferred haloalkyl groups are $-CF_3$ and $-CCl_3$. Particularly preferred haloalkoxy groups are $-OCF_3$ and $-OCCl_3$.

As used herein, a heteroaryl group is typically a 5- to 10-membered aromatic ring, such as a 5- or 6-membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include

pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, thiazolyl, imidazolyl and pyrazolyl groups. Pyridyl, thienyl, isoxazolyl and furanyl groups are preferred. A heteroaryl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substitutents on a heteroaryl group include halogen, C_{1-6} alkyl, C_{2-7} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro, cyano, carbamoyl, mono(C_{1-6} alkyl)carbamoyl, di(C_{1-6} alkyl)carbomyl, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, $-CO_2R'$, $-CONR'R''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)NR'R''$, $-NH-S(O)_2R'$ or $-NH-CO-R'$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl.

Preferred substituents on a heteroaryl group include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

As used herein, references to a heteroaryl group include fused ring systems in which a heteroaryl group is fused to a monocyclic said aryl, carbocyclyl or heterocyclyl group, or to a further heteroaryl group. Preferred such ring systems are those wherein a heteroaryl group is fused to an aryl group, for example a phenyl group. An example of such a fused ring system is a group wherein a thienyl group is fused to a phenyl ring to form a benzothienyl group.

Typically, R^1 is C_{1-6} alkyl or aryl. Preferably, R^1 is C_{1-2} alkyl or phenyl. More preferably, R^1 is phenyl.

Typically, R^2 is hydrogen or C_{1-4} alkyl. Preferably, R^2 is hydrogen.

Typically, R^3 is halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino or di(C_{1-4} alkyl)amino. Preferably, R^3 is fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, amino, mono(C_{1-2} alkyl)amino or di(C_{1-2} alkyl)amino. More preferably, R^3 is methyl, trifluoromethyl, fluorine, chlorine or bromine. Most preferably, R^3 is chlorine.

Typically, n is 0, 1 or 2. Preferably, n is 0 or 1.

Typically, R^4 is hydrogen or C_{1-4} alkyl. Preferably, R^4 is hydrogen or C_{1-2} alkyl. More preferably, R^4 is hydrogen.

When R^5 is a heterocyclyl group, it is typically attached via a carbon atom. Typically, R^5 is C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-XR^6$. Preferably, R^5 is C_{1-4} alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C_{1-2} alkyl)-, for example benzyl, heteroaryl-(C_{1-2} alkyl)- or $-XR^6$. More preferably, R^5 is C_{1-4} alkyl, phenyl, thienyl, furanyl, isoxazolyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, phenyl-CH_2-, furanyl-CH_2- or $-XR^6$. Most preferably, R^5 is phenyl-CH_2-, furanyl-CH_2- or $-XR^6$.

Typically, X is -CO-, -S(O)- or $-S(O)_2$-. Preferably, X is -CO- or $-S(O)_2$-.

When R^6 is a group $-NR'R''$ and either R' or R'' includes an aryl, heteroaryl, carbocyclyl or heterocyclyl moiety it is typically unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro and cyano. Preferably, the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro. More preferably, the aryl, heteroaryl, carbocyclyl or heterocyclyl moiety is unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent. When R' or R'' is a heteroaryl or heterocyclyl group, it is attached via a carbon atom.

Typically, R' and R'' are not both hydrogen. Typically, each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl, carbocyclyl, aryl-(C_{1-4} alkyl)- or heteroaryl-(C_{1-4} alkyl)-. Preferably, each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, phenyl-CH_2-, cyclohexyl or cyclopentyl. More preferably, one of R' and R'' represents hydrogen. Most preferably, one of R' and R'' is hydrogen and the other is C_{1-4} alkyl, phenyl, phenyl-CH_2-, cyclohexyl or cyclopentyl.

Typically, R^6 is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-NR'R''$ wherein R' and R'' are as defined above. Preferably, R^6 is C_{1-4} alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example N-heterocyclyl, phenyl-(C_{1-2} alkyl)-, for example benzyl, heteroaryl-(C_{1-2} alkyl)- or $-NR'R''$ wherein R' and R'' are as defined above. More preferably, R^6 is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl, or $-NR'R''$ wherein R' and R'' are as defined above.

Preferred compounds of the invention are those in which:

- R^1 is C_{1-6} alkyl or aryl;
- R^2 is hydrogen or C_{1-4} alkyl;
- R^3 is halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino or di(C_{1-4} alkyl)amino or, preferably, R^3 is fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, amino, mono(C_{1-2} alkyl)amino or di (C_{1-2} alkyl)amino;
- n is 0, 1 or 2;
- R^4 is hydrogen or C_{1-4} alkyl;
- R^5 is C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-XR^6$;
- X is -CO-, -S(O)- or $-S(O)_2-$; and
- R^6 is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl, carbocyclyl, aryl-(C_{1-4} alkyl)- or heteroaryl-(C_{1-4} alkyl)-,

the aryl, heteroaryl, carbocyclyl and heterocyclyl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1, 2 or 3 substituents selected from

halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano.

Preferably, in these preferred compounds of the invention, the aryl, heteroaryl and carbocyclyl moieties in the groups R' and R'' are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro and cyano.

Further preferred compounds of the invention are those wherein:

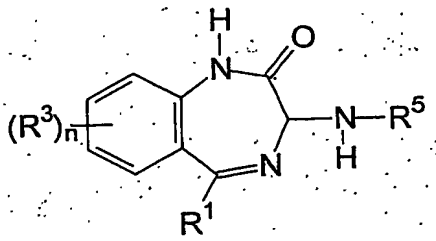
- R^1 is C_{1-2} alkyl or phenyl;
- R^2 is hydrogen or C_{1-4} alkyl;
- R^3 is methyl, trifluoromethyl, fluorine, chlorine or bromine;
- n is 0 or 1;
- R^4 is hydrogen or C_{1-2} alkyl;
- R^5 is C_{1-4} alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example piperidinyl, morpholinyl and piperazinyl, phenyl-(C_{1-2} alkyl)-, for example benzyl, heteroaryl-(C_{1-2} alkyl)- or $-XR^6$, provided that when R^5 is heterocyclyl it is attached via a carbon atom;
- X is -CO-, -S(O)- or $-S(O)_2-$; and
- R^6 is C_{1-4} alkyl, aryl, for example phenyl and dihydrobenzofuranyl, heteroaryl, for example thienyl, furanyl, isoxazolyl, pyridyl and benzothienyl, carbocyclyl, for example cyclopentyl and cyclohexyl, heterocyclyl, for example N-heterocyclyl, phenyl-(C_{1-2} alkyl)-, for example benzyl, heteroaryl-(C_{1-2} alkyl)- or $-NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-,

the aryl, heteroaryl, carbocyclyl and heterocyclyl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1 or 2 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano.

Preferably, in these further preferred compounds of the invention, the cyclohexyl, cyclopentyl and phenyl moieties in the groups R' and R'' are

unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

Particularly preferred compounds of the invention are compounds of formula (Ia) and pharmaceutically acceptable salts thereof



(Ia)

wherein:

- R^1 is phenyl or methyl;
- R^3 is chlorine;
- n is 0 or 1;
- R^5 is phenyl-CH_2-, furanyl-CH_2- or -XR^6;
- X is -CO- or -$S(O)_2$-; and
- R^6 is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl, or -$NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-,

the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

Preferably, in these particularly preferred compounds of the invention, the cyclohexyl, cyclopentyl and phenyl moieties of the groups R' and R'' are unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

Compounds of the formula (I) containing one or more chiral centre may be used in enantiomerically or diasteroisomerically pure form, or in the form of

a mixture of isomers. For the avoidance of doubt, the compounds of the formula (I) can, if desired, be used in the form of solvates.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutical acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of formula (I) include:

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

1,1-Diethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide;

2,2-Dimethyl-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide;

Cyclopentanecarboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Cyclohexanecarboxylic acid 2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

3-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

4-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-trifluoromethyl-benzamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

Thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-amide;

Furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Piperidine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Morpholine-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

4-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

3-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

4-Methyl-piperazine-1-carboxylic acid -(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

3,4-Dichloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-trifluoromethyl-benzamide;

4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

2-Nitro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

Benzo[b]thiophene-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

2,3-Dihydro-benzofuran-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Isoxazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Benzo[b]thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Thiophen-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isonicotinamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide;
Propane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
Butane-1-sulfonic acid--(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
2-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;
3-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;
4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;
2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide;
3-(2-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
3-(3-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
3-(4-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
3-(2-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
3-(3-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
5-Phenyl-3-(2-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
5-Phenyl-3-(3-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
5-Phenyl-3-(4-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
3-[(Furan-2-ylmethyl)-amino]-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one;
N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;
N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide;
N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide;

Furan-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Thiophene-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

Cyclohexanecarboxylic acid (7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-methoxy-benzamide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-methoxy-benzamide;

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-nitro-benzamide;

2-(2-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(3-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(4-Methoxy-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(4-Nitro-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

2-(3-Nitro-phenyl)N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-trifluoromethyl-phenyl)-acetamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(3-trifluoromethyl-phenyl)-acetamide;

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide;

1-(2-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(2-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

1-(4-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea;

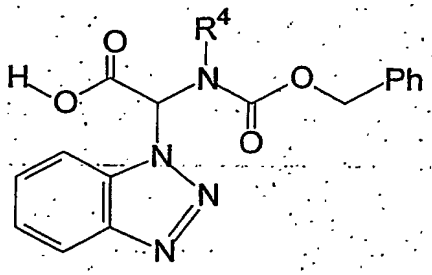
1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-p-tolyl-urea;

1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea; and

1-(4-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea,

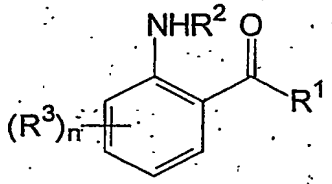
and pharmaceutically acceptable salts thereof.

Compounds of formula (I) may be prepared by reacting glyoxylic acid ($HCO\text{-}CO_2H$), benzotriazole and an appropriate benzyl carbamate at reflux in toluene, under Dean-Stark conditions giving the key protected amino acid of formula (II)



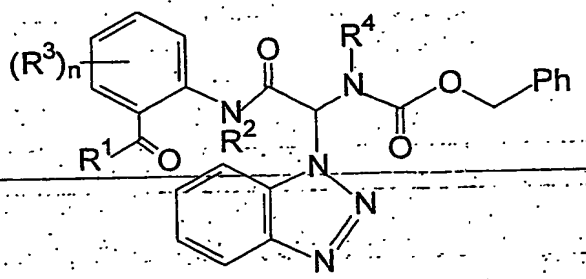
(II)

The thus obtained amino acid of formula (II) can then be reacted with a suitable chlorinating agent, such as oxalyl chloride, followed by reaction with a 2-aminobenzophenone of formula (III)



(III)

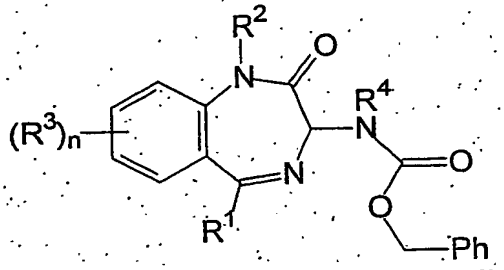
to give the intermediate amide of formula (IV).



(IV)

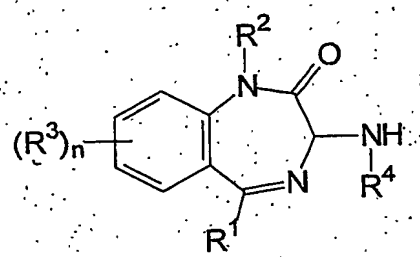
which need not be characterized.

The compound of formula (IV) can then be subjected to ammonolysis followed by ring closure in acetic acid containing ammonium acetate to obtain the protected benzodiazepine of formula (V)



(V)

The compound of formula (V) can then be deprotected using hydrogen bromide in acetic acid to yield the deprotected amine of formula (VI).



(VI)

Compounds of formula (I), in which R^5 is XR^6 and X is -CO- can be prepared by reacting a compound of formula (VI), as defined above, with an acid anhydride in a suitable solvent, preferably pyridine at ambient temperature, or with an acid chloride in a suitable solvent in the presence of a base, preferably in THF at ambient temperature with triethylamine present.

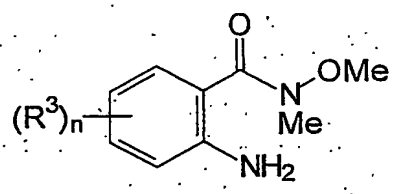
If the acid chloride used is an amino carbonyl chloride, the compound of formula (I) is a tertiary urea. In the case where R^6 is NH-R', such compounds may be prepared by the reaction of a compound of formula (VI) with an isocyanate. This reaction is preferably carried out in THF at ambient temperature. Alternatively, the isocyanate may be prepared *in situ* from the relevant amine and phosgene, in the presence of a base, usually triethylamine, again in THF.

Compounds of formula (I), in which R^5 is $-XR^6$ and X is $-S(O)_2-$ may be prepared by the reaction of a compound of formula (VI) with a suitable sulfonyl chloride. Similarly, compounds of formula (I), in which R^5 is XR^6 and X is -S(O)- may be prepared by the reaction of a compound of formula (VI) with a suitable sulfinyl chloride

Compounds of formula (I) in which R^5 is not XR^6 may be prepared by known methods. For example, a compound of formula (VI) can be reacted with a compound of formula R^5-L, wherein L is a leaving group such as a chlorine atom, a mesylate group or a triflate group. When R^5 is aryl or heteroaryl, L can be $-B(OH)_2$ and the reaction may take place in the presence of copper acetate. Such boronic acid coupling reactions will, of course, be familiar to those of skill in the art. Compounds wherein R^5 is aryl or heteroaryl may also be prepared by way of a Buchwald reaction or by reaction of a compound of formula (VI) with an appropriate fluoroaryl or fluoroheteroaryl compound. Compounds wherein R^5 is a heteroaryl group may also be prepared by reaction of a compound of formula (VI) with a suitable chloroheteroaryl or bromoheteroaryl compound. Compounds wherein R^5 is a carbocyclyl group may also be prepared by known methods, for example a compound wherein R^5 is cyclohexyl may be prepared by the reaction of a compound of formula (VI) with cyclohexanone in the presence of a reducing agent.

Compounds of formula (I) in which the R^5 group is aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- can also be prepared by the reaction of a compound of formula (VI) with an aldehyde in the presence of a reducing agent. Preferably, such reactions between compounds of formula (VI) and aldehydes are carried out in a mixture of dichloromethane and acetic acid in the presence of sodium (triacetoxy)borohydride at ambient temperature.

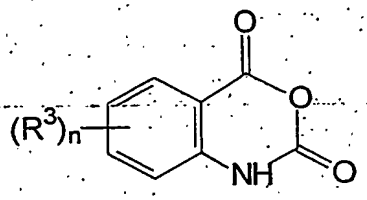
In the preparation of the benzodiazepine skeleton, commercially available aminobenzophenone compounds of formula (III) can be used where possible. Compounds of formula (III) which are not commercially available can be prepared by known methods, for example by reaction of a Weinreb type amide of formula (VII)



(VII)

with a group R^1-Li or a Grignard reagent such as R^1-MgBr. Preferably this reaction is carried out in THF at –100°C.

Compounds of formula (VII) are known compounds or can be prepared by analogy with known methods. For example, they can be prepared from the reaction of isatoic anhydrides of formula (VIII)



(VIII)

with N,O-dimethyl hydroxylamine under standard reaction conditions.

The starting materials of formula (II), (III), (VII), and (VIII) are known compounds, or may be prepared by analogy with known methods.

Further synthetic manipulation of the thus obtained compounds of formula (I) may be carried out by conventional methods to achieve further compounds of formula (I). The benzodiazepines of formula (I) can be salified by treatment with an appropriate acid or base.

As explained above, the compounds of the invention are active against RSV. The present invention therefore provides a method for treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

RSV is prevalent among children younger than two years of age. It is a particularly serious risk amongst any such children who suffer from chronic lung disease. Accordingly, the said medicament is typically for use in treating a patient who is a child under two years of age. Typically, said child suffers from chronic lung disease.

Further, anti-RSV prophylaxis is recommended for infants born at 32 weeks of gestation or earlier, until they reach 6 months of age. Accordingly, the said medicament is typically for use in preventing RSV infection in an infant less than 6 years of age, who was born after 32 weeks of gestation or less.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

In a preferred embodiment, the compounds of the invention are administered by intranasal or intrabronchial administration. The present invention also provides an inhaler or nebuliser containing a medicament which comprises (a) a benzodiazepine derivative of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

The present invention also provides a pharmaceutical composition containing such a benzodiazepine derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

The compounds of the invention are typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in

general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

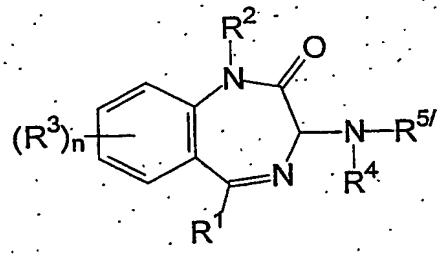
Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

Certain benzodiazepine derivatives of the formula (I) are novel *per se*. The present invention includes these novel compounds and pharmaceutically acceptable salts thereof. The present invention therefore also provides compounds of formula (Ib) and pharmaceutically acceptable salts thereof



(Ib)

wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- $R^{5'}$ represents C_{2-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-X'$, provided that when $R^{5'}$ is heteroaryl it is not 2-quinaldyl or 6-chloro-pyrazinyl and when $R^{5'}$ is heteroaryl-(C_{1-6} alkyl)- it is not 2-indolylmethyl or 2-(3-indolyl)ethyl;
- X' represents $-CO-R^{6'}$, $-S(O)-R^{6''}$ or $-S(O)_2-R^{6'''}$;
- $R^{6'}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that (a) when $R^{6'}$ is aryl it is not unsubstituted naphthyl, unsubstituted phenyl, mono-halophenyl, 4-methylphenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-*n*-propylphenyl, 4-*t*-butylphenyl, 4-*n*-pentylphenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 3-trifluoromethylthiophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl or 2,3,4,5,6-pentafluorophenyl, (b) when $R^{6'}$ is heteroaryl it is not 2-pyrrolyl, 2-pyrazinyl, 2-quinaldyl, 2-methyl-indolyl, 2-benzofuranyl, 2-benzothienyl, 3-thienyl, 3-indolyl, unsubstituted 2-indolyl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-bromoindol-2-yl, 5-hydroxyindol-2-yl or 5-methoxyindol-2-yl, (c) when $R^{6'}$ is aryl-(C_{1-6} alkyl)- it is not 4-thianaphthene-(CH_2)-, (d) when $R^{6'}$ is heteroaryl-(C_{1-6} alkyl)- it is not -indolyl-$(CH_2)_x$-, wherein x is 1, 2, 3, and (e) when R' is hydrogen, R'' is not

4-halophenyl, 3-methylphenyl, 3-cyanophenyl, 3-aminophenyl, 3-aminocarbonylphenyl, 3-benzoic acid, 3-benzoic acid ethyl ester, 6-amino-3-pyridyl, 5-(2-chloro)pyridyl, 5-(2-methoxy)pyridyl, 5-indanyl or benzotriazol-3-yl;

- $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-; and

- $R^{6///}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that when $R^{6///}$ is aryl it is not 4-methylphenyl.

Preferred R^1, R^2, R^3 and R^4 groups in the formula (Ib) include those preferred groups set out above as preferred R^1, R^2, R^3 and R^4 groups in the formula (I).

Typically, in the formula (Ib), R^2 is hydrogen.

Preferred compounds of formula (Ib) are those in which:

- $R^{5/}$ represents C_{2-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-X^{/}$, provided that when $R^{5/}$ is heteroaryl it is not quinaldyl or pyrazinyl and when $R^{5/}$ is heteroaryl-(C_{1-6} alkyl)- it is not indolyl-$(CH_2)_x$-, wherein x is 1 or 2.;
- $X^{/}$ represents $-CO-R^{6/}$, $-S(O)-R^{6//}$ or $-S(O)_2-R^{6///}$;
- $R^{6/}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that (a) when $R^{6/}$ is aryl it is not phenyl or naphthyl, (b) when $R^{6/}$ is heteroaryl it is not thienyl, pyrrolyl, pyrazinyl, quinaldyl, indolyl, benzofuranyl or benzothienyl, (c) when $R^{6/}$ is aryl-(C_{1-6} alkyl)- it is not thianaphthene-(CH_2)-, (d) , when $R^{6/}$ is heteroaryl-(C_{1-6} alkyl)- it is

not indolyl-$(CH_2)_x$-, wherein x is 1, 2, 3, and (e) when R' is hydrogen, R'' is not phenyl, pyridyl, indanyl or benzotriazolyl;

- $R^{6''}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-; and

- $R^{6'''}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that when $R^{6'''}$ is aryl it is not methylphenyl.

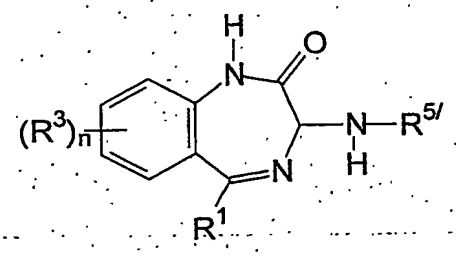
Further preferred compounds of formula (Ib) are those where:

- $R^{5'}$ is C_{2-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl), heterocyclyl-(C_{1-6} alkyl) or $-X'$;
- X' is $-CO-R^{6'}$, $-S(O)-R^{6''}$ or $-S(O)_2-R^{6'''}$;
- $R^{6'}$ is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or heterocyclyl;
- $R^{6''}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-; and
- $R^{6'''}$ is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-.

Preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl and carbocyclyl moieties in the groups $R^{5/}$, $R^{6/}$, $R^{6//}$ and $R^{6///}$ are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro and cyano,

More preferably, in said further preferred compounds of formula (Ib), the cycloalkyl, heterocyclyl, carbocyclyl, aryl and heteroaryl moieties in the groups $R^{/}$ and $R^{//}$ are unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, nitro and cyano.

Particularly preferred novel compounds of the present invention are compounds of formula (Ic) and pharmaceutically acceptable salts thereof



(Ic)

wherein:

- R^1 is phenyl or methyl;
- R^3 is chlorine;
- n is 0 or 1;
- $R^{5/}$ is phenyl-CH_2-, furanyl-CH_2- or -$X^{/}$;
- $X^{/}$ is -CO-$R^{6/}$, -CO-$NR^{/}R^{//}$, -$S(O)_2$-$R^{6///}$ or -$S(O)_2$-$NR_{/}R_{//}$;
- $R^{6/}$ is C_{1-4} alkyl, 2-thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, 3-benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl;
- $R^{6///}$ is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl or piperazinyl, for example N-piperazinyl;

- each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-, and
- each $R_{/}$ and $R_{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-.

the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R^5 and $R^{6/}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the group $R^{6///}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the phenyl moiety in the group $R^{6///}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{2-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the cyclohexyl and cyclopentyl moieties in the groups $R^{/}$ and $R^{//}$ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent,

the phenyl moiety in the groups $R^{/}$ and $R^{//}$ being unsubstituted or substituted by a single methoxy or nitro substituent, and

the phenyl, cyclohexyl and cyclopentyl moieties in the groups $R_{/}$ and $R_{//}$ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

Further preferred novel compounds of the present invention are compounds of formula (Ic), and pharmaceutically acceptable salts thereof, where:

- $R^{5/}$ is -$X^{/}$;
- $X^{/}$ is -CO-$R^{6/}$, -CO-$NR^{/}R^{//}$, -$S(O)_2$-$R^{6///}$ or -$S(O)_2$-$NR_{/}R_{//}$;
- $R^{6/}$ is C_{1-4} alkyl, pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl;

- $R^{6///}$ is C_{1-4} alkyl, pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, for example N-piperidinyl, morpholinyl, for example N-morpholinyl, piperazinyl, for example N-piperazinyl;
- each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl or cyclopentyl; and
- each $R_{/}$ and $R_{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-,

the pyridyl, cyclopentyl, cyclohexyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl, piperazinyl moieties in the groups $R^{6/}$ and $R^{6///}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro, and

the phenyl, cyclohexyl and cyclopentyl moieties in the groups $R^{/}$, $R^{//}$, $R_{/}$ and $R_{//}$ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

The present invention also relates to the novel compounds, as defined above, or a pharmaceutically acceptable salt thereof, for use in a method of treating the human or animal body. The present invention also relates to a pharmaceutical composition comprising a novel compound as defined above and a pharmaceutically acceptable diluant or carrier.

The following Examples illustrate the invention. They do not however, limit the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of anti-RSV activity. There are many assays available to determine the activity of given compounds against RSV, and a negative result in any one particular assay is therefore not determinative.

EXAMPLES

In this section, all temperatures are in °C. Flash column chromatography was carried out using Merck 9385 silica. Solid phase extraction (SPE) chromatography was carried out using Jones Chromatography (Si) cartridges under 15mmHg vacuum with stepped gradient elution. Thin layer chromatography (TLC) was carried out on plastic plates.

LC-MS CONDITIONS

Samples were run on a MicroMass ZMD, using electrospray with simultaneous positive – negative ion detection.

Column : YMC-PACK FL-ODS AQ, 50 x 4.6mm I.D S-5μm.

Gradient : 95:5 to 5:95 v/v H_2O/CH_3CN + 0.05% Formic Acid over 4.0 min, hold 3 min, return to 95:5 v/v H_2O/CH_3CN + 0.05% Formic Acid over 0.2 min and hold at 95:5 v/v H_2O/CH_3CN + 0.05% Formic Acid over 3 min.

Detection : PDA 250 – 340 nm.

Flow rate : 1.5 ml/min

Preparation Intermediate 1

Benzotriazol-1-yl-benzyloxycarbonylamino-acetic acid

A mixture of glyoxylic acid monohydrate (4.60g), benzotriazole (5.95g) and benzyl carbamate (7.55g) was heated to reflux in toluene (100ml) for 18h, under Dean-Stark conditions. The mixture was then allowed to cool to room temperature, and the resulting precipitate collected by filtration. This was then recrystallised from diethyl ether giving an off-white solid (11.66g)

^{1}H NMR (d6 DMSO, δ) 5.07 (q+s, 3H) 7.25 (d, 1H) 7.3-7.63 (m,6H) 7.92-8.10 (m, 2H) 9.32 (d, 1H)

LC/MS Found ES- = 325 RT= 4.68min

Preparation Intermediate 2

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester

A cold (0°C) solution of Intermediate 1 (11.6g) in dry THF (100ml) under nitrogen was stirred, and was treated dropwise with a solution of oxalyl chloride (4.4g) in dry dichloromethane (50ml), followed by dry dimethylformamide (2ml). This resulting mixture was stirred for 2h, and was then treated with a solution of 2-(amino-phenyl)-phenyl-methanone (6.1g) and N-methylmorpholine (7.07g) in dry THF (50ml) over 30 minutes. The reaction mixture was then allowed to warm to room temperature and was then filtered to remove inorganic salts. The mother liquors were then treated with 7M ammonia in methanol (100ml) and stirring continued for 18h. The solvents were then evaporated and the residue partitioned between ethyl acetate and 1M sodium hydroxide. The dried extracts were evaporated, and the crude oil dissolved in acetic acid (200ml) containing ammonium acetate (13.4g). This mixture was then stirred at room temperature for 18h. The solvents were then evaporated and the residue was suspended in ethyl acetate:diethyl ether (1:3) (200ml): 1M sodium hydroxide was added until pH8 was reached, and then the mixture was cooled to 0-5°C and the resulting solid collected by filtration (6.94g)

^{1}H NMR (d6 DMSO, δ) 5.05 (s, 1H) 5.09 (m, 2H) 7.25-7.69 (m,14H) 8.38 (d, 1H) 10.85 (s, 1H)
LC/MS Found ES+ = 386 RT= 5.46min

Preparation Intermediate 3

3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Intermediate 2 (1.07g) was dissolved in 48% hydrobromic acid in acetic acid (30ml) and was heated to 70°C for 30mins. The mixture was then allowed to cool, and was diluted with diethyl ether (30ml). This led to the formation of a yellow solid which

was collected by filtration. This material was then partitioned between ethyl acetate and 1M potassium carbonate solution. The extracts were dried, and then evaporated giving an oil which was triturated with diethyl ether giving an off-white solid (0.35g) ^{1}H NMR (d6 DMSO, δ) 4.25 (s, 1H) 7.17-7.66 (m, 9H) 10.65 (brs, 1H) LC/MS RT= 3.23min, but with no associated molecular ion.

Preparation Intermediate 4

[Benzotriazol-1-yl(2-benzoyl-4-chloro-phenylcarbamoyl)-methyl]-carbamic acid benzyl ester

The acid chloride of Intermediate 1 was prepared as previously described from 5g of Intermediate 1. This was added to a stirred solution of (2-amino-5-chloro-phenyl)-phenyl-methanone (3.48g) and N-methylmorpholine (3.1g) in THF (40ml) at 0°C. After addition the mixture was allowed to warm to room temperature, and was stirred for 1h. The precipitate was removed by filtration, and the solvent evaporated giving a gummy solid, which was used without purification or characterisation.

Preparation Intermediate 5

(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid benzyl ester

A solution of Intermediate 4 in 7M ammonia in methanol (100ml) was stirred at room temperature for 5h. The solvent was evaporated, and the residue partitioned between ethyl acetate, and 1M sodium hydroxide. The dried organic layer was evaporated, and the residue dissolved in acetic acid (200ml) containing ammonium acetate (5.8g). The resulting mixture was stirred at room temperature for 18h, and then the solvent was evaporated. The residue was dissolved in water and ethyl acetate, and the pH was adjusted to ca.8 with sodium hydroxide. The dried organic extracts were evaporated, and the residue triturated with diethyl ether giving a beige solid (3.27g).

LC/MS Found ES+ = 420,422 ($C_{23}H_{13}ClN_3O_3$ = 419.5)

Preparation Intermediate 6

5-Amino-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

A solution of Intermediate 5 (3.25g) in 45% hydrogen bromide in acetic acid (85ml) was heated to 70°C for 2h. The mixture was then allowed to cool, and was diluted with diethyl ether. The hydrobromide salt of the title compound was obtained by filtration and dried, giving a bright yellow solid (2.7g)

NMR (δ, d6 DMSO) 5.18 (d, 1H) 7.32 (d, 1H) 7.40 (d, 1H) 7.47-7.53 (m, 5H) 7.77 (dd, 1H) 9.07 (brs, 2H) 11.41 (s, 1H)

Example 1

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

A solution of Intermediate 3 (300mg) in pyridine (5ml) was treated with acetic anhydride (183mg). The mixture was stirred at room temperature for 1.5h and was then evaporated. The residue was partitioned between water and dichloromethane. The dried extract was evaporated and the residue triturated with petroleum ether giving a colourless solid (231mg)

LC/MS RT=3.82 min Found ES- = 292

NMR (δ, d6 DMSO) 1.99 (s, 3H) 5.25 (d, 1H) 7.21-7.66 (m, 9H) 9.06 (s, 1H) 10.81 (s, 1H).

Example 2

1,1-Diethyl-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

A solution of Intermediate 3 (100mg) in dichloromethane:dimethylformamide (9:1; 2ml) containing diisopropylethylamine (62mg) was treated with diethylcarbamoyl chloride (0.05ml). The resulting mixture was stirred under nitrogen at room temperature for 18h, and was then partitioned between water and dichloromethane. The organic extract was evaporated and the residue was purified on a silica gel SPE cartridge. Elution with 10% methanol in ethyl acetate gave a colourless solid (34mg).

LC/MS RT=4.37 min Found ES+ = 351

^{1}H NMR (d6 DMSO, δ) 1.11 (t,6H) 2.50 (br,4H) 5.20 (d,1H) 6.83 (d,1H) 7.20-7.66 (m,9H) 10.78 (brs,1H)

Example 3

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

This material was prepared as described for Example 2 except that propionyl chloride (0.035ml) was used. The title compound was a colourless solid (11mg)

LC/MS RT= 4.03min Found ES+ =308

^{1}H NMR (d6 DMSO, δ) 1.03 (t,3H) 2.31 (q,2H) 5.26 (d,1H) 7.20-7.67 (m,9H) 8.94 (d,1H) 10.80 (s,1H)

Example 4

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide

This material was prepared as described for Example 2 except that butyryl chloride (0.041ml) was used. The title compound was a colourless solid (31mg)

LC/MS RT= 4.31min Found ES+ =320

^{1}H NMR (d6 DMSO, δ) 0.90 (brt,3H) 1.55 (br,2H) 2.27 (brq,2H) 5.26 (brd,1H) 7.20-7.70 (m,9H) 8.95 (brd,1H) 10.80 (s,1H)

Example 5

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide

This material was prepared as described for Example 2 except that isobutyryl chloride (41ml) was used. The title compound was a colourless solid (35mg)
LC/MS RT= 4.30min Found ES+ =322

^{1}H NMR (d6 DMSO, δ) 1.03 (d,6H) 2.72 (septet,1H) 5.23 (d,1H) 7.20-7.68 (m,9H) 8.90 (d,1H) 10.77 (brs,1H)

Example 6

2,2-Dimethyl-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide

This material was prepared as described for Example 2 except that 2,2-dimethylpropionyl chloride (0.049ml) was used. The title compound was a colourless solid (22mg)

LC/MS RT= 4.74min Found ES+ =336
^{1}H NMR (d6 DMSO, δ) 1.20 (s,9H) 5.23 (d,1H) 7.20-7.68 (m,9H) 8.22 (d,1H) 10.80 (br,1H)

Example 7

Cyclopentanecarboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that cyclopentanecarbonyl chloride (0.048ml) was used. The title compound was a colourless solid (40mg).

LC/MS RT=4.81 min Found ES+ =348

^{1}H NMR (d6 DMSO, δ) 1.48-1.90 (m,8H) 2.89 (m,1H) 5.24 (d,1H) 7.20-7.68 (m,9H) 8.90 (d,1H) 10.77 (brs,1H)

Example 8

Cyclohexanecarboxylic acid 2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that cyclohexanecarbonyl chloride (0.053ml) was used. The title compound was a colourless solid (57mg).

LC/MS RT=5.54 min Found ES+ =362

^{1}H NMR (d6 DMSO, δ) 1.10-1.43 (5H) 1.60-1.82 (m,5H) 2.44 (m,1H) 5.22 (d,1H) 7.20-7.67 (m,9H) 8.81 (d,1H) 10.75 (s,1H)

Example 9

3-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 1 except that 3-methoxy-benzoyl chloride (0.056ml) was used. The title compound was a colourless solid (23mg).

LC/MS RT= 5.10min Found ES+ =386

^{1}H NMR (d6 DMSO, δ) 3.84 (s,3H) 5.51 (d,1H) 7.11-7.71 (m,13H) 9.51 (d,1H) 10.87 (s,1H)

Example 10

4-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 4-methoxy-benzoyl chloride (68mg) was used. The title compound was a colourless solid (60mg).

LC/MS RT= 5.00min Found ES+ =386

^{1}H NMR (d6 DMSO, δ) 3.83 (s,3H) 5.50 (d,1H) 7.02 (d,2H) 7.21-7.79 (m,9H) 8.02 (d,2H) 9.28 (d,1H) 10.85 (s,1H)

Example 11

2-Methoxy N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 2-methoxy-benzoyl chloride (0.059ml) was used. The title compound was a colourless solid (69mg).

LC/MS RT= 5.12min Found ES+ =386

^{1}H NMR (d6 DMSO, δ) 4.05 (s,3H) 5.44 (d,1H) 7.11 (t,1H) 7.24-7.70 (,m11H) 7.97 (dd,1H) 9.50 (d,1H) 10.97 (s,1H)

Example 12

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-trifluoromethyl-benzamide

This material was prepared as described for Example 2 except that 3-trifluoromethyl-

benzoyl chloride (0.06ml) was used. The title compound was a colourless solid (88mg).

LC/MS RT=5.27 min Found ES+ =424

^{1}H NMR (d6 DMSO, δ) 5.41 (d,1H) 7.22-7.82 (m,13H) 9.71 (d,1H) 10.86 (brs,1H)

Example 13

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that benzoyl chloride (0.046ml) was used. The title compound was a colourless solid (41mg).

LC/MS RT= 4.96min Found ES+ =356

^{1}H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.22-7.70 (m,12H) 8.03 (m,2H) 9.44 (d,1H) 10.87 (s,1H)

Example 14

Thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-amide

This material was prepared as described for Example 2 except that thiophene-2-carbonyl chloride (0.043ml) was used. The title compound was a colourless solid (81mg).

LC/MS RT= 4.87min Found ES+ =362

^{1}H NMR (d6 DMSO, δ) 5.46 (d,1H) 7.19-7.82 (m,11H) 8.20 (m,1H) 9.57 (d,1H) 10.88 (s,1H)

Example 15

Furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that furan-2-carbonyl chloride (0.039ml) was used. The title compound was a colourles solid (17mg).

LC/MS RT=4.53 min Found ES+ =346

^{1}H NMR (d6 DMSO, δ) 5.42 (d,1H) 6.68 (m,1H) 7.24-7.70 (m,10H) 7.90 (m,1H) 9.02 (d,1H) 10.95 (s;1H)

Example 16

Piperidine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that piperidine-1-carbonyl chloride (0.049ml) was used. The title compound was a colourless solid (34mg).

LC/MS RT= 4.47min Found ES+ =363

^{1}H NMR (d6 DMSO, δ) 1.40-1.62 (m,6H) 3.36-3.42 (m,4H) 5.21 (d,1H) 7.20-7.67 (m,10H) 10.76 (s,1H)

Example 17

Morpholine-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that morpholine-4-carbonyl chloride (0.046ml) was used. The title compound was a colourless solid

(22mg).

LC/MS RT= 3.88min Found ES+ =365

^{1}H NMR (d6 DMSO, δ) 3.36-3.42 (m,4H) 3.55-3.62 (m,4H) 5.21 (d,1H) 7.22-7.67 (m,10H) 10.80 (s,1H)-

Example 18

4-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 4-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (90mg).

LC/MS RT=5.25 min Found ES+ =401

^{1}H NMR (d6 DMSO, δ) 5.50 (d,1H) 7.23-7.70 (m,9H) 8.25 (d,2H) 8.33 (d,2H) 9.94 (d,1H) 10.92 (s,1H)

Example 19

3-Nitro- N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 3-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (94g).

LC/MS RT= 5.25min Found ES+ =401

^{1}H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.22-7.85 (m,10H) 8.40-8.48 (m,2H) 8.86 (m,1H) 10.06 (d,1H) 10.91 (s,1H)

Example 20

4-Methyl-piperazine-1-carboxylic acid -(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that 4-methyl-1-piperazinecarbonyl chloride (79mg) was used. The title compound was a colourless solid (35mg).

LC/MS RT329= min Found ES- =376

^{1}H NMR (d6 DMSO, δ) 2.19 (s,3H) 2.28 (m,4H) 3.40 (m,4H) 5.19 (d,1H) 7.19-7.65 (m,10H) 10.75 (s,1H)

Example 21

3,4-Dichloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 3,4-dichloro-benzoyl chloride (83mg) was used. The title compound was a colourless solid (42mg).

LC/MS RT=3.29 min Found ES+ =424, 426

^{1}H NMR (d6 DMSO, δ) 5.48 (d,1H) 7.22-7.70 (m,9H) 7.78 (d,1H) 7.98 (dd,1H) 8.31 (d,1H) 9.82 (d,1H) 10.91 (s,1H)

Example 22

N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-trifluoromethyl-benzamide

This material was prepared as described for Example 2 except that 2-trifluoromethyl-benzoyl chloride (83mg) was used. The title compound was a colourless solid (90mg).

LC/MS RT= 5.47min Found ES+ =424

^{1}H NMR (d6 DMSO, δ) 5.41 (d,1H) 7.25-7.83 (m,13H) 9.81 (d,1H) 10.93 (s,1H)

Example 23

4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 4-bromo-benzoyl chloride (87mg) was used. The title compound was a colourless solid (159mg).
LC/MS RT=5.76 min Found ES+ =434, 436

^{1}H NMR (d6 DMSO, δ) 5.5 (d,1H) 7.23-7.68 (m,9H) 7.72 (d,2H) 7.98 (d,2H) 9.7 (d,1H) 10.94 (s,1H)

Example 24

2-Methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 2-methyl-benzoyl chloride (62mg) was used. The title compound was a colourless solid (113mg).

LC/MS RT= 5.29min Found ES+ =370
^{1}H NMR (d6 DMSO, δ) 2.42 (s,3H) 5.45 (d,1H) 7.23-7.55 (m,12H) 7.65 (dt,1H) 9.39 (d,1H) 10.90 (s,1H)

Example 25

2-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide
This material was prepared as described for Example 2 except that 2-chloro-benzoyl chloride (70mg) was used. The title compound was a colourless solid (108mg).
LC/MS RT= 5.28min Found ES+ =390, 392

^{1}H NMR (d6 DMSO, δ) 5.43 (d,1H) 7.26-7.7 (m,13H) 9.71 (d,1H) 10.94 (s,1H)

Example 26

2-Nitro-N-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as described for Example 2 except that 2-nitro-benzoyl chloride (74mg) was used. The title compound was a colourless solid (50mg).

LC/MS RT=4.94 min Found ES+ =401

^{1}H NMR (d6 DMSO, δ) 5.42 (d, 1H) 7.25-7.89 (m, 12H) 8.07 (d,1H) 10.05 (d, 1H) 10.96 (s, 1H)

Example 27

Benzo[b]thiophene-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that benzo[b]thiopehene-3-carbonyl chloride (39mg) was used. The title compound was a colourless solid (60mg).

LC/MS RT= 5.85min Found ES+ =412

^{1}H NMR (d6 DMSO, δ) 5.57 (d, 1H) 7.27-7.71 (m, 11H) 8.06 (m, 1H) 8.47 (m, 1H) 8.83 (s, 1H) 9.57 (d, 1H) 10.95 (s, 1H)

Example 28

2,3-Dihydro-benzofuran-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that 2,3-dihydro-benzofuran-5-carbonyl chloride (36mg) was used. The title compound was a colourless solid (75mg).

LC/MS RT= 5.16min Found ES+ =398

^{1}H NMR (d6 DMSO, δ) 3.24 (t, 2H) 4.61 (t, 2H) 5.48 (d, 1H) 6.84 (d,1H) 7.22-7.95 (m,11H) 9.25 (d,1H) 10.89 (s,1H)

Example 29

Isoxazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that isoxazole-5-carbonyl chloride (26mg) was used. The title compound was a colourless solid (22mg).

LC/MS RT= 4.58min Found ES+ =347

^{1}H NMR (d6 DMSO, δ) 5.44 (d,1H) 7.23-7.72 (m, 10H) 8.80 (d, 1H) 9.98 (d,1H) 11.03 (s,1H)

Example 30

Benzo[b]thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that benzo[b]thiophene-2-carbonyl chloride (39mg) was used. The title compound was a colourless solid (33mg).

LC/MS RT=5.90 min Found ES+ =412

^{1}H NMR (d6 DMSO, δ) 5.49 (d,1H) 7.25-7.72 (m,11H) 7.95-8.07 (m,2H) 8.56 (s,1H) 9.92 (d,1H) 10.96 (s,1H)

Example 31

Thiophen-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that thiophene-3-carbonyl chloride (29mg) was used. The title compound was a colourless solid (30mg).

LC/MS RT= 4.96min Found ES+ =362

^{1}H NMR (d6 DMSO, δ) 5.47 (d,1H) 7.23-7.70 (m,11H) 8.48 (m,1H) 9.40 (d,1H) 10.91 (s,1H)

Example 32

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isonicotinamide

This material was prepared as described for Example 2 except that isonicotinoyl chloride, hydrochloride (71mg) was used as well as an extra equivalent of triethylamine. The title compound was a colourless solid (22mg).

LC/MS RT= 3.98min Found ES+ =357

^{1}H NMR (d6 DMSO, δ) 5.50 (d,1H) 7.24-7.70 (m,9H) 7.93 (d,2H) 8.76 (d,2H) 9.89 (d,1H) 10.91 (s,1H)

Example 33

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

This material was prepared as described for Example 2 except that nicotinoyl chloride, hydrochloride was used as well as an extra equivalent of triethylamine. The title compound was a colourless solid (16mg).

LC/MS RT= 3.90min Found ES+ =357

^{1}H NMR (d6 DMSO, δ) 5.51 (d,1H) 7.23-7.70 (m,10H) 8.37 (ddd,1H) 8.75 (dd,1H) 9.15 (d,1H) 9.90 (d,1H) 10.93 (s,1H)

Example 34

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide

This material was prepared as described for Example 2 except that methanesulfonyl chloride (0.031ml) was used. The title compound was a colourless solid (40mg).

LC/MS RT= 4.20min Found ES+ =330

^{1}H NMR (d6 DMSO, δ) 3.13 (s,3H) 4.81 (brd,1H) 7.22-7.70 (m,9H) 8.43 (brd,1H) 10.95 (brs,1H)

Example 35

Propane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that propane-1-sulfonyl chloride (0.054ml) was used. The title compound was a colourless solid (56mg).

LC/MS RT= 4.79min Found ES+ =358

^{1}H NMR (d6 DMSO, δ) 1.03 (t,3H) 1.84 (m,2H) 3.14 (t,2H) 4.79 (d,1H) 7.23-7.69 (m,9H) 8.49 (d,1H) 10.94 (s,1H)

Example 36

Butane-1-sulfonic acid-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-

yl)-amide

This material was prepared as described for Example 2 except that butane-1-sulfonyl chloride (0.062ml) was used. The title compound was a colourless solid (30mg).

LC/MS RT= 5.18min Found ES+ =372

^{1}H NMR (d6 DMSO, δ) 0.93 (t,3H) 1.44 (m,2H) 1.80 (m,2H) 3.14 (t,2H) 4.78 (brd,1H) 7.21-7.68 (m,9H) 8.47 (brd,1H) 10.94 (brs,1H)

Example 37

2-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 2 except that 2-bromo-benzenesulfonyl chloride (122mg) was used. The title compound was a colourless solid (137mg).

LC/MS RT= 5.53min Found ES+ =470, 472

^{1}H NMR (d6 DMSO, δ) 4.95 (s,1H) 7.03-7.71 (m,12H) 7.88 (m,1H) 8.22 (m,1H) 8.70 (br,1H) 11.04 (s,1H)

Example 38

3-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 2 except that 3-bromo-benzenesulfonyl chloride (122mg) was used. The title compound was a colourless solid (90mg).

LC/MS RT=5.63 min Found ES+ =470, 472

^{1}H NMR (d6 DMSO, δ) 4.81 (s,1H) 6.89 (m,2H) 7.20-7.70 (m,9H) 7.82 (m,1H) 7.94

(m,1H) 9.3 (br,1H) 10.97 (s,1H)

Example 39

4-Bromo-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 2 except that 4-bromo-benzenesulfonyl chloride (122mg) was used. The title compound was a colourless solid (130mg).

LC/MS RT= 5.66min Found ES+ =470, 472

^{1}H NMR (d6 DMSO, δ) 4.80 (brd,1H) 6.75 (m,2H) 7.20-7.70 (m,7H) 7.78-7.91 (m,4H) 9.40 (brd,1H) 10.95 s,1H)

Example 40

2-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzenesulfonamide

This material was prepared as described for Example 1 except that 2-fluoro-benzenesulfonyl chloride (93mg) was used. The title compound was a colourless solid (140mg).

LC/MS RT= 5.26min Found ES+ =410

^{1}H NMR (d6 DMSO, δ) 4.94 (d,1H) 7.07 (m,2H) 7.23-7.97 (m,11H) 9.36 (d,1H) 10.97 (s,1H)

Example 41

3-(2-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

A solution of Intermediate 3 (50mg) and sodium (triacetoxy)borohydride (106mg) in dichloromethane (6ml) and acetic acid (1ml) was treated with 2-nitro-benzaldehyde (45mg). The resulting mixture was stirred under nitrogen for 18h. Saturated sodium bicarbonate solution was carefully added, and the mixture extracted with dichloromethane. The organic layer was passed through a hydrophobic frit, and evaporated. The residue was then purified on a silica gel SPE cartridge. Gradient elution with 10-18% ethyl acetate in petrol gave the title compound as a colourless solid (33mg)

LC/MS RT=4.83 min Found ES+ =387

^{1}H NMR (d6 DMSO, δ) 3.4 (br, 1H) 4.17 (brs, 1H) 4.31 (q, 2H) 7.15-7.95 (m, 13H) 10.74 (s, 1H)

Example 42

3-(3-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 3-nitro-benzaldehyde (45mg) was used. The title compound was a colourless solid (32mg).

LC/MS RT=4.95 min Found ES+ =387

^{1}H NMR (d6 DMSO, δ) 3.45 (br, 1H) 4.16 (brs, 1H) 4.23 (brm, 2H) 7.15-7.63 (m, 10H) 7.85 (d, 1H) 8.08 (dd, 1H) 8.30 (s, 1H) 10.76 (s, 1H)

Example 43

3-(4-Nitro-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 4-nitro-benzaldehyde (45mg) was used. The title compound was a colourless solid (33mg).

LC/MS RT=4.88 min Found ES+ =387

^{1}H NMR (d6 DMSO, δ) 3.42 (br, 1H) 4.11-4.30 (brm, 3H) 7.16-7.63 (m, 9H) 7.70 (d, 2H) 8.20 (d, 2H) 10.77 (s, 1H)

Example 44

3-(2-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 2-methoxy-benzaldehyde (41mg) was used. The title compound was a colourless solid (48mg).

LC/MS RT=4.95 min Found ES+ =372
^{1}H NMR (d6 DMSO, δ) 3.73 (s, 3H) 3.97 (q, 2H) 4.17 (s, 1H) 6.85-6.96 (m, 2H) 7.15-7.63 (m, 11H) 10.72 (s, 1H)

Example 45

3-(3-Methoxy-benzylamino)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 3-methoxy-benzaldehyde (41mg) was used. The title compound was a colourless solid (43g).

LC/MS RT=5.03 min Found ES+ =372
^{1}H NMR (d6 DMSO, δ) 3.71 (s, 3H) 3.81-4.18 (m, 3H) 6.74 (m, 1H) 6.80-6.86 (m, 2H) 7.15-7.64 (m, 10H) 10.74 (s, 1H)

Example 46

5-Phenyl-3-(2-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 2-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless

solid (29mg).

LC/MS RT=5.02 min Found ES+ =410

^{1}H NMR (d6 DMSO, δ) 4.18 (s, 1H) 4.23 (brs, 2H) 7.15-7.70 (m, 12H) 7.91 (d, 1H) 10.76 (s, 1H)

Example 47

5-Phenyl-3-(3-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 3-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless solid (34mg).

LC/MS RT= 5.28min Found ES- =408

^{1}H NMR (d6 DMSO, δ) 4.12 (q, 2H) 4.18 (s, 1H) 7.15-7.78 (m, 13H) 10.74 (s, 1H)

Example 48

5-Phenyl-3-(4-trifluoromethyl-benzylamino)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 4-trifluoromethyl-benzaldehyde (52mg) was used. The title compound was a colourless solid (25mg).

LC/MS RT= 5.27min Found ES-408 =

^{1}H NMR (d6 DMSO, δ) 4.13 (q, 2H) 4.20 (s, 1H) 7.15-7.70 (m, 13H) 10.76 (s, 1H)

Example 49

3-[(Furan-2-ylmethyl)-amino]-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

This material was prepared as described for Example 41 except that 2-furaldehyde (29mg) was used. The title compound was a colourless solid (56mg).

LC/MS RT=4.07 min Found ES+ =332

^{1}H NMR (d6 DMSO, δ) 3.05 (m, 1H) 3.80-4.13 (m, 2H) 4.18 (d, 1H) 6.19 (brs, 1H) 6.32 (brs, 1H) 7.15-7.65 (m, 10H)

Example 50

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 1 except that Intermediate 6 (mg) was used. The title compound was a colourless solid (17mg).

LC/MS RT=4.21 min Found ES+ =328, 330

^{1}H NMR (d6 DMSO, δ) 3.34 (s, 3H) 5.26 (d, 1H) 7.28-7.31 (m, 2H) 7.31-7.58 (m, 5H) 7.71 (dd, 1H) 9.14 (d, 1H) 10.96 (s, 1H)

Example 51

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-isobutyramide

This material was prepared as described for Example 2 except that Intermediate 6 (0.021ml) was used and isobutyl chloride. The title compound was a colourless solid (49mg).

LC/MS RT=4.78 min Found ES+ =356, 358

^{1}H NMR (d6 DMSO, δ) 1.04 (d, 6H) 2.72 (septet, 1H) 5.27 (d, 1H) 7.29-7.55 (m,7H) 7.71 (dd, 1H) 9.00 (d, 1H) 10.92 (s, 1H)

Example 52

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-methanesulfonamide

This material was prepared as described for Example 2 except that Intermediate 6 and methanesulfonyl chloride (0.015ml) were used. The title compound was a colourless solid (18mg).

LC/MS RT= 4.61min Found ES+ =364, 366
^{1}H NMR (d6 DMSO, δ) 3.13 (s,3H) 4.85 (brd, 1H) 7.29-7.58 (m, 7H) 7.71 (dd, 1H) 8.46 (brd, 1H) 11.04 (brs, 1H)

Example 53

Furan-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example except that Intermediate 6 and 2-furancarbonyl chloride (0.020ml) were used. The title compound was a colourless solid (50mg).

LC/MS RT=5.07 min Found ES+ =380, 382
^{1}H NMR (d6 DMSO, δ) 5.45 (d, 1H) 6.68 (m, 1H) 7.28-7.70 (m, 7H) 7.73 (dd, 1H) 7.91 (m,1H) 9.15 (d, 1H) 11.07 (s, 1H)

Example 54

Thiophene-2-carboxylic acid (7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-

benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that Intermediate 6 and 2-thiophenecarbonyl chloride (0.021ml) were used. The title compound was a colourless solid (49mg).

LC/MS RT=5.40 min Found ES+ =396, 398

^{1}H NMR (d6 DMSO, δ) 5.49 (d, 1H) 7.22-7.83 (m, 10H) 8.21 (dd, 1H) 9.67 (d, 1H) 11.04 (s, 1H)

Example 55

Cyclohexanecarboxylic acid (7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as described for Example 2 except that Intermediate 6 and cyclohexanecarbonyl chloride (0.027) were used. The title compound was a colourless solid (52mg).

LC/MS RT=5.61 min Found ES+ =396, 398

^{1}H NMR (d6 DMSO, δ) 1.2-1.33 (m, 5H) 1.60-1.83 (m, 5H) 2.45 (m, 1H) 5.25 (d, 1H) 7.27-7.73 (m, 8H) 8.93 (d, 1H) 10.92 (s, 1H)

Example 56

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-methoxy-benzamide

This material was prepared as described for Example 2 except that Intermediate 6 and 2-methoxy-benzoyl chloride (0.030ml) were used. The title compound was a colourless solid (55mg).

LC/MS RT=5.58 min Found ES+ =420, 422

^{1}H NMR (d6 DMSO, δ) 4.05 (s,3H) 5.47 (d, 1H) 7.12 (t, 1H) 7.25-7.61 (m, 9H) 7.72 (dd, 1H) 7.98 (dd,1H) 9.54 (d,1H) 11.14 (s, 1H)

Example 57

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-methoxy-benzamide

This material was prepared as described for Example 2 except that Intermediate 6 and 4-methoxy-benzoyl chloride (0.027ml) were used. The title compound was a colourless solid (61mg).

LC/MS RT=5.48 min Found ES+ =420, 422

^{1}H NMR (d6 DMSO, δ) 3.84 (s, 3H) 5.53 (d, 1H) 7.03 (d, 2H) 7.31-7.59 (m, 8H) 8.04 (d, 2H) 9.39 (d, 1H) 11.01 (s, 1H)

Example 58

N-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-nitro-benzamide

This material was prepared as described for Example 2 except that Intermediate 6 and 2-nitro-benzoyl chloride (0.027) were used. The title compound was a colourless solid (61mg).

LC/MS RT=5.25 min Found ES+ =435, 437

^{1}H NMR (d6 DMSO, δ) 5.45 (d, 1H) 7.36-7.88 (m, 11H) 8.07 *d, 1H) 10.03 (d, 1H) 11.03 (s, 1H)

Example 59

2-(2-Methoxy-phenyl)N- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (2-methoxy-phenyl)-acetyl chloride (33mg) was used. The title compound was a colourless solid (13mg).

LC/MS RT=4.98 min Found ES+ =400
^{1}H NMR (d6 DMSO, δ) 3.63 (s, 2H) 3.79 (s, 3H) 5.25 (d, 1H) 6.89-6.99 (m, 2H) 7.20-7.33 (m, 5H) 7.45-7.68 (m, 6H) 9.01 (d, 1H) 10.87 (s, 1H)

Example 60

2-(3-Methoxy-phenyl)N- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (3-methoxy-phenyl)-acetyl chloride (33mg) was used. The title compound was a colourless solid (12mg).

LC/MS RT=4.95 min Found ES+ =400
^{1}H NMR (d6 DMSO, δ) 3.62 (m, 2H) 3.75 (s, 3H) 5.23 (d, 1H) 6.78-6.96 (m, 3H) 7.19-7.70 (m, 10H) 9.33 (d, 1H) 10.86 (s, 1H)

Example 61

2-(4-Methoxy-phenyl)N- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (4-methoxy-

phenyl)-acetyl chloride (33mg) was used. The title compound was a 2colourless solid (20mg).

LC/MS RT=4.86 min Found ES+ =400

^{1}H NMR (d6 DMSO, δ) 3.58 (s, 2H) 3.73 (s, 3H) 5.22 (d, 1H) 6.87 (d, 2H) 7.23-7.71 (m, 11H) 9.25 (d, 1H) 10.85 (s, 1H)

Example 62

2-(4-Nitro-phenyl)N- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (4-nitro-phenyl)-acetyl chloride (36mg) was used. The title compound was a colourless solid (18mg).

LC/MS RT=5.03 min Found ES+ =415

^{1}H NMR (d6 DMSO, δ) 3.86 (s, 2H) 5.24 (d, 1H) 7.24-7.70 (m, 11H) 8.19 (d, 2H) 9.53 (d, 1H) 10.88 (s, 1H)

Example 63

2-(3-Nitro-phenyl)N- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-acetamide

This material was prepared as described for Example 2 except that (3-nitro-phenyl)-acetyl chloride (36mg) was used. The title compound was a colourless solid (25mg).

LC/MS RT=5.02 min Found ES+ =415

^{1}H NMR (d6 DMSO, δ) 3.86 (s, 2H) 5.24 (d, 1H) 7.24-7.67 (m, 10H) 7.89 (d, 1H) 8.12 (dd, 1H) 8.26 (s, 1H) 9.53 (d, 1H) 10.89 (s, 1H)

Example 64

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-trifluoromethyl-phenyl)-acetamide

This material was prepared as described for Example 2 except that (2-trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a colourless solid (9mg).

LC/MS RT= 5.43min Found ES+ =438

^{1}H NMR (d6 DMSO, δ) 3.92 (s, 2H) 5.26 (d, 1H) 7.24-7.70 (m, 13H) 9.41 (d, 1H) 10.87 (s, 1H)

Example 65

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(3-trifluoromethyl-phenyl)-acetamide

This material was prepared as described for Example 2 except that 3-trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a colourless solid (20mg).

LC/MS RT= 5.56min Found ES+ =438

^{1}H NMR (d6 DMSO, δ) 3.80 (s, 2H) 5.24 (d, 1H) 7.24-7.75 (m, 13H) 9.49 (d, 1H) 10.89 (s, 1H)

Example 66

N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide

This material was prepared as described for Example 2 except that (4-

trifluoromethyl-phenyl)-acetyl chloride (41mg) was used. The title compound was a colourless solid (13mg).

LC/MS RT= 5.57min Found ES+ =438

^{1}H NMR (d6 DMSO, δ) 3.79 (s, 2H) 5.23 (d, 1H) 7.24-7.70 (m, 13H) 9.48 (d, 1H) 10.87 (s, 1H)

Example 67

1-(2-Methoxy-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

A solution of 2-methoxy-aniline (37mg) in dry dichloromethane (3ml) was treated with triethylamine (0.04ml) followed by 20% phosgene in toluene (0.08ml). The mixture was stirred at room temperature for 1h, and then Intermediate 3 (37mg) was then added, and the stirring continued for 18h. The mixture was partitioned between water and ethyl acetate. The organic layer was passed through a hydrophobic frit and evaporated and the residue was purified on a silica gel SPE cartridge. Gradient elution with 0-5% methanol in dichloromethane gave the title compound as a colourless solid (24mg).

LC/MS RT=5.05 min Found ES+ =401

^{1}H NMR (d6 DMSO, δ) 3.86 (s, 3H) 5.21 (d, 1H) 6.78-7.02 (m, 3H) 7.23-7.70 (m, 9H) 7.98 (m 1H) 8.26 (d, 1H) 8.60 (s, 1H) 10.89 (s, 1H)

Example 68

1-(2-Nitro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

This material was prepared as described for Example 67 except that 2-nitro-aniline (21mg) was used. The title compound was a yellow solid (23mg).

LC/MS RT=5.30 min Found ES+ =416

^{1}H NMR (d6 DMSO, δ) 5.19 (d, 1H) 7.15-7.70 (m, 11H) 8.05 (dd, 1H) 8.17 (d, 1H) 8.82 (d,1H) 9.68 (s, 1H) 10.95 (s, 1H)

Example 69

1-(2-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

This material was prepared as described for Example 67 except that 2-chloro-aniline (0.017 ml) was used. The title compound was a colourless solid (21mg).

LC/MS RT=5.34 min Found ES+ =405

^{1}H NMR (d6 DMSO, δ) 5.21 (d, 1H) 6.94-7.70 (m, 12H) 8.08 (m, 1H) 8.47 (d, 1H) 8.57 (s, 1H) 10.93 (s, 1H)

Example 70

1-(4-Chloro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

A mixture of Intermediate 3 (30mg) and 4-chloro-1-isocyanato-benzene (0.011ml) in dry THF (4ml) was treated with triethylamine (0.05ml). The mixture was stirred at room temperature for 18h, and was then partitioned between water and dichloromethane. The organic layer was passed through a hydrophobic frit, and was then evaporated. The residue was triturated with petroleum ether giving the title compound as a beige solid (34mg).

LC/MS RT= 5.45min Found ES+ =405

^{1}H NMR (d6 DMSO, δ) 5.17 (d, 1H) 7.25-7.70 (m, 14H) 9.18 (s, 1H) 10.95 (s, 1H)

Example 71

1-(2- oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-p-tolyl-urea

This material was prepared as described for Example 70 except that 1-isocyanato-4-methyl-benzene (0.011ml) was used. The title compound was a off-white solid (32mg).

LC/MS RT=5.18 min Found ES+ =385

^{1}H NMR (d6 DMSO, δ) 2.22 (s, 3H) 5.19 (d, 1H) 7.05 (d, 2H) 7.23-7.70 (m, 12H) 8.92 (s, 1H) 10.92 (s, 1H)

Example 72

1-(2-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

This material was prepared as described for Example 70 except that 2-flyoro-1-isocyanato-benzene (0.010 ml) was used. The title compound was a beige solid (29mg).

LC/MS RT= 5.09min Found ES+ =389

^{1}H NMR (d6 DMSO, δ) 5.21 (d, 1H) 6.90-7.70 (m, 12H) 8.07 (m, 2H) 8.93 (s, 1H) 10.94 (s, 1H)

Example 73

1-(4-Fluoro-phenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea

This material was prepared as described for Example 70 except that 4-fluoro-1-isocyanato-benzene (0.010ml) was used. The title compound was an off-white solid (26mg).

LC/MS RT= 5.02min Found ES+ =389

^{1}H NMR (d6 DMSO, δ) 5.18 (d, 1H) 7.08 (t, 2H) 7.25-7.70 (m, 12H) 9.07 (s, 1H) 10.94 (s, 1H)

Activity Example 1

XTT Assay Protocol

The inner 60 wells of 96 well tissue culture plates were seeded with Vero cells at $3x10^4$ cells/well ($1x\ 10^4$ cells/well for toxicity studies) in 100 or 150 µl of medium and incubated at 37°C overnight or until nearing confluency. For primary screen, 25 µl compounds were added directly to 100 µl medium in single wells to duplicate plates. A third plate was prepared for simultaneous toxicity investigation.

For follow up investigation, 70 µl of compound in duplicate wells were added directly to culture medium at 3.2x final concentration and ½ log serially diluted down columns of plate. A duplicate plate was prepared for simultaneous toxicity investigation.

Cells were infected with 25 µl RSV to give m.o.i. ≈ 0.2. Some 100 µl of sterile distilled water were added to the outer wells of the plate and incubated at 33°C for 6 days. Some 0.25 µl/ml PMS were added to stock XTT solution, final conc. 25 µM PMS. Then 25 µl warmed XTT/PMS solution were added to each well and incubated for 5 hours at 37°C. Plates were shaken (DynaTech Vari-Shaker) vigorously for 10 mins and allowed to cool for 15 mins before sealing. Absorbance at 450 nM was measured and data analysed using Microsoft Excel software.

Maximum OD_{450nm} reading (uninfected, untreated control cells) corresponded to 100% inhibition. Minimum OD_{450nm} readings (infected control cells) corresponded to 0% inhibition. Log10 concentration was plotted against OD_{450nm} and IC_{50} (Table 1) values were calculated from either reading 50% value from graph or using regression analysis.

Table 1

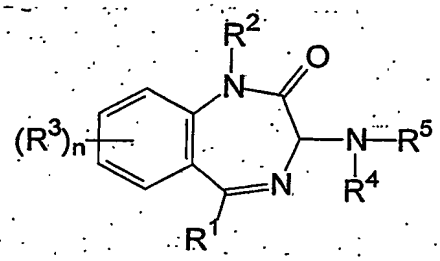
Example	XTT IC50 (uM)	TD50 (2d)	TD50 (6d)
1			
2	4		
3	2.5		
4	5		
5	2.5		
6	6		
7	2		
8	2		
9	2	70	100
10	1.5		
11	0.5	100	
12	2.5		
13	1.5	100	
14	1.5	100	
15	1		
16	2		
17	5		
18	2		
19	2	100	100
20	25		
21	6	100	100
22	4		
23	5		
24	3		
25	2		
26	2		
27	5		
28	2		
29	3		
30	5		
31	2		
32	2.5		
33	3		

34	6		
35	15		
36	15		
37	6	50	40
38	10	60	50
39	10	50	15
40	10	100	100
41	20		
42	30		
43	10		
44	20		
45	30		
46	30	100	50
47		100	50
48	50	100	100
49	50		
50	5		
51	3		
52	5		
53	1.5		30
54	3		30
55	5		
56	0.7		
57	1.2		30
58	5		
59	5		
60	3		
61	1.5		
62	1.7		
63	1		
64	2		100
65	1.5		30
66	1.5		100
67	1		
68	1.5		
69	1.5		100
70	3		50

71	1.5		100
72	1		100
73	1.5		100

CLAIMS

1. Use of a benzodiazepine derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or preventing an RSV infection



(I)

wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- R^5 represents C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-XR^6$;
- X represents -CO-, -S(O)- or $-S(O)_2-$; and
- R^6 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-.

2. Use according to claim 1, wherein R^1 is C_{1-2} alkyl or aryl.

3. Use according to any one of the preceding claims wherein R^2 is hydrogen.

4. Use according to any one of the preceding claims wherein R^3 is halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, amino, mono(C_{1-4} alkyl)amino or di(C_{1-4} alkyl)amino.

5. Use according to claim 4, wherein R^3 is fluorine, chlorine, bromine, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} alkylthio, C_{1-2} haloalkyl, C_{1-2} haloalkoxy, amino, mono(C_{1-2} alkyl)amino or di (C_{1-2} alkyl)amino.

6. Use according to any one of the preceding claims wherein R^4 is hydrogen.

7. Use according to any one of the preceding claims wherein R^5 is C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-XR^6$.

8. Use according to claim 7, wherein R^5 is C_{1-4} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, phenyl-(C_{1-2} alkyl)-, heteroaryl-(C_{1-2} alkyl)- or $-XR^6$.

9. Use according to claim 8, wherein R^5 is C_{1-4} alkyl, phenyl, thienyl, furanyl, isoxazolyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, phenyl-CH_2-, furanyl-CH_2- or $-XR^6$.

10. Use according to any one of the preceding claims wherein X is -CO- or $-S(O)_2$-.

11. Use according to any one of the preceding claims wherein, when R^6 is a group $-NR'R''$ wherein each R' and R'' is the same or different and represents

hydrogen, C_{1-4} alkyl, aryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)- or heteroaryl-(C_{1-4} alkyl)-.

12. Use according to claim 11, wherein when R^6 is a group $-NR'R''$ each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, phenyl, phenyl-CH_2-, cyclohexyl or cyclopentyl.

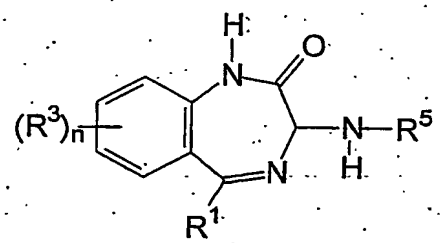
13. Use according to claim 12, wherein when R^6 is a group $-NR'R''$ and one of R' and R'' is hydrogen.

14. Use according to any one of the preceding claims wherein R^6 is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-4} alkyl)-, heteroaryl-(C_{1-4} alkyl)-, carbocyclyl-(C_{1-4} alkyl)-, heterocyclyl-(C_{1-4} alkyl)- or $-NR'R''$.

15. Use according to claim 14, wherein R^6 is C_{1-4} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, phenyl-(C_{1-2} alkyl)-, heteroaryl-(C_{1-2} alkyl)- or $-NR'R''$.

16. Use according to claim 15, wherein R^6 is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl, piperazinyl or $-NR'R''$.

17. Use according to any one of the preceding claims wherein the benzodiazepine derivative of formula (I) is a benzodiazepine derivative of formula (Ia):



(Ia)

wherein:

- R^1 is phenyl or methyl;
- R^3 is chlorine;
- n is 0 or 1;
- R^5 is phenyl-CH_2-, furanyl-CH_2- or -XR^6;
- X is -CO- or -$S(O)_2$-;
- R^6 is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl, piperazinyl or -$NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-,

the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R^5 and R^6 being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro.

18. Use according to any one of the preceding claims, wherein the medicament is for use in treating a patient who is a child under two years of age.

19. Use according to claim 18 wherein said child suffers from chronic lung disease.

20. Use according to any one of claims 1 to 17 wherein the medicament is for use in preventing RSV infection in an infant less than six years of age who was born after 32 weeks of gestation or less.

21. Use according to any one of the preceding claims, wherein the medicament is suitable for intranasal or intrabronchial administration.

22. A method of treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective

amount of a benzodiazepine derivative of formula (I), as defined in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof.

23. A method according to claim 22, wherein said patient is a patient as defined in any one of claims 18 to 20.

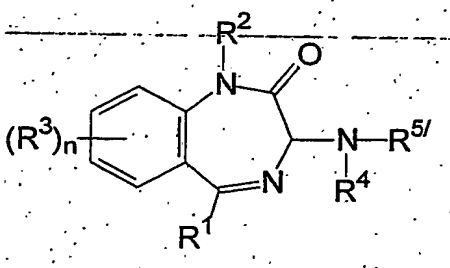
24. A method according to claim 22 or 23, wherein the benzodiazepine derivative or salt thereof is administered intranasally or intrabronchially.

25. An inhaler or nebuliser containing a medicament which comprises

(a) a benzodiazepine derivative of formula (I), as defined in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, and

(b) a pharmaceutically acceptable carrier or diluent.

26. A benzodiazepine derivative of formula (Ib), or a pharmaceutically acceptable salt thereof



(Ib)

wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;

- R^4 represents hydrogen or C_{1-6} alkyl;
- $R^{5/}$ represents C_{2-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or -$X^/$, provided that when $R^{5/}$ is heteroaryl it is not 2-quinaldyl or 6-chloro-pyrazinyl and when $R^{5/}$ is heteroaryl-(C_{1-6} alkyl)- it is not 2-indolylmethyl or 2-(3-indolyl)ethyl;
- $X^/$ represents -CO-$R^{6/}$, -S(O)-$R^{6//}$ or -$S(O)_2$-$R^{6///}$;
- $R^{6/}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or -$NR^/R^{//}$ wherein each $R^/$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that (a) when $R^{6/}$ is aryl it is not unsubstituted naphthyl, unsubstituted phenyl, mono-halophenyl, 4-methylphenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-cyanophenyl, 4-*n*-propylphenyl, 4-*t*-butylphenyl, 4-*n*-pentylphenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 3-trifluoromethylthiophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl or 2,3,4,5,6-pentafluorophenyl, (b) when $R^{6/}$ is heteroaryl it is not 2-pyrrolyl, 2-pyrazinyl, 2-quinaldyl, 2-methyl-indolyl, 2-benzofuranyl, 2-benzothienyl, 3-thienyl, 3-indolyl, unsubstituted 2-indolyl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-bromoindol-2-yl, 5-hydroxyindol-2-yl or 5-methoxyindol-2-yl, (c) when $R^{6/}$ is aryl-(C_{1-6} alkyl)- it is not 4-thianaphthene-(CH_2)-, (d) when $R^{6/}$ is heteroaryl-(C_{1-6} alkyl)- it is not 3-indolyl-$(CH_2)_x$-, wherein x is 1, 2, 3, and (e) when $R^/$ is hydrogen, $R^{//}$ is not 4-halophenyl, 3-methylphenyl, 3-cyanophenyl, 3-aminophenyl, 3-aminocarbonylphenyl, 3-benzoic acid, 3-benzoic acid ethyl ester, 6-amino-3-pyridyl, 5-(2-chloro)pyridyl, 5-(2-methoxy)pyridyl, 5-indanyl or benzotriazol-3-yl;
- $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or -$NR^/R^{//}$ wherein

each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-; and

- $R^{6///}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-, provided that when $R^{6///}$ is aryl it is not 4-methylphenyl.

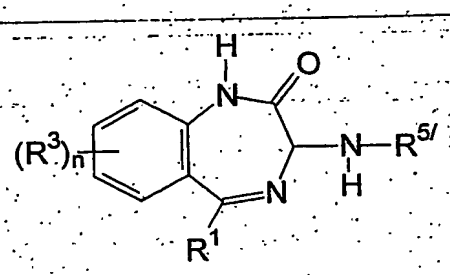
27. A benzodiazepine derivative according to claim 26 wherein:

- $R^{5/}$ is C_{2-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl), heterocyclyl-(C_{1-6} alkyl) or $-X^{/}$;
- $X^{/}$ is $-CO-R^{6/}$, $-S(O)-R^{6//}$ or $-S(O)_2-R^{6///}$;
- $R^{6/}$ is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or heterocyclyl;
- $R^{6//}$ represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-; and
- $R^{6///}$ is C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, heterocyclyl, C_{3-6} cycloalkyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR^{/}R^{//}$ wherein each $R^{/}$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-(C_{1-6} alkyl)- or heteroaryl-(C_{1-6} alkyl)-.

28. A benzodiazepine derivative according to claim 26 or claim 27 wherein R^2 is

hydrogen.

29. A benzodiazepine derivative of formula (Ic), or a pharmaceutically acceptable salt thereof,



(Ic)

wherein:

- R^1 is phenyl or methyl;
- R^3 is chlorine;
- n is 0 or 1;
- $R^{5/}$ is phenyl-CH_2-, furanyl-CH_2- or -$X^/$;
- $X^/$ is -CO-$R^{6/}$, -CO-$NR^/R^{//}$, -$S(O)_2$-$R^{6///}$ or -$S(O)_2$-$NR_/R_{//}$;
- $R^{6/}$ is C_{1-4} alkyl, 2-thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, 3-benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl, piperazinyl;
- $R^{6///}$ is C_{1-4} alkyl, phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl morpholinyl, or piperazinyl;
- each $R^/$ and $R^{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-, and
- each $R_/$ and $R_{//}$ is the same or different and represents hydrogen, C_{1-4} alkyl, cyclohexyl, cyclopentyl, phenyl or phenyl-CH_2-

the phenyl, thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the groups R^5 and $R^{6/}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the thienyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, benzothienyl, dihydrobenzofuranyl, isoxazolyl, piperidinyl, morpholinyl and piperazinyl moieties in the group $R^{6'''}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the phenyl moiety in the group $R^{6'''}$ being unsubstituted or substituted by 1 or 2 substituents selected from fluorine, chlorine, bromine, C_{2-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and nitro,

the cyclohexyl and cyclopentyl moieties in the groups R' and R'' being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent,

the phenyl moiety in the groups R' and R'' being unsubstituted or substituted by a single methoxy or nitro substituent, and

the phenyl, cyclohexyl and cyclopentyl moieties in the groups $R_{/}$ and $R_{//}$ being unsubstituted or substituted by a single fluoro, chloro, methyl, methoxy or nitro substituent.

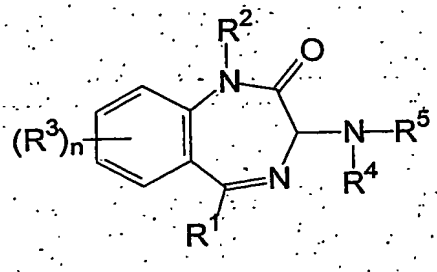
30. A benzodiazepine derivative according to any one of claims 26 to 29 for use in a method of treating the human or animal body.

31. A pharmaceutical composition comprising a benzodiazepine derivative according to any one of claims 26 to 29, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluant or carrier.

ABSTRACT

CHEMICAL COMPOUNDS

Benzodiazepine derivative of formula (I), and pharmaceutically acceptable salts thereof, are found to be active against RSV



(I)

wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$ or $-S(O)NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- R^5 represents C_{1-6} alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-XR^6$;
- X represents -CO-, -S(O)- or $-S(O)_2$-; and
- R^6 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-(C_{1-6} alkyl)-, heteroaryl-(C_{1-6} alkyl)-, carbocyclyl-(C_{1-6} alkyl)-, heterocyclyl-(C_{1-6} alkyl)- or $-NR'R''$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl or aryl.

PCT Application
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